REMARKS

Applicants request reconsideration of the above-identified application in view of the foregoing proposed amendments and following remarks, which place the claims in better form for allowance or appeal (37 C.F.R. § 1.116(b)).

Applicants have amended claims 16-17 and 19-21 and added new dependent claim 22. New claim 22 simply recites subject matter that was previously presented in claim 20. Claim 22 neither adds new matter nor requires the Examiner to consider the subject matter for the first time. Therefore, the claims now pending in this application are claims 16-17 and 19-22.

Applicants have adopted the Examiner's suggestion by amending claim 16 to delete the semicolon from line 15 of the claim. In addition, applicants have amended claims 16 and 17 to improve their form and to more particularly point out and distinctly claim the subject matter which applicants regard as the invention. For example, amended claims 16 and 17 now recite a step of using all or part of a binding pocket of the of the unphosphorylated JNK3 to design or select an inhibitor. Support for the term "inhibitor" can be found throughout the specification as originally filed, e.g., at page 1, lines 19-23; page 3, lines 11-14; page 4, lines 2-3; page 8, lines 28-

30, page 18, lines 26-28; page 21, lines 28-30; page 22, lines 29-33; page 24, line 35 to page 25, line 4; page 26, lines 1-18; page 29, line 34 to page 30, line 20; and Examples 5-6. Support for the term "unphosphorylated" can be found throughout the specification as originally filed, e.g., at page 3, lines 1-4, page 6, lines 26-29. And, support for the term "all or part of" can be found in the specification at page 21, lines 18-36.

Applicants have also deleted recitation of the term "JNK3 mutant molecule" from claims 16, 17 and 19. These amendments are being made without waiver of applicants' rights to continue to prosecute and to obtain claims directed to the deleted subject matter either in this application or in other applications, including divisional or continuing applications, claiming benefit herefrom under 35 U.S.C. § 120.

Applicants have amended claim 20 to independent form and to incorporate all of the elements of claim 16. Applicants have amended claim 21 to depend from claim 20. Finally, applicants have added claim 22, which is directed to an unphosphorylated JNK3 molecule further containing an N-terminal deletion of 39 amino acids.

None of the proposed amendments or added claims presents new matter.

The Objection

The Examiner has objected to former claim 16 as ending with both a semicolon and a period. Applicants have adopted the Examiner's suggestion to correct the typographical error of the semicolon, thus rendering moot this objection.

The Rejections

35 U.S.C. § 112, Second Paragraph: Indefiniteness

Claims 16, 17 and 19-21 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. In particular, the Examiner asserts that the limitation of "wherein all or part of the atomic coordinates ... are determined to comprise a binding pocket..." causes the claim to be vague and indefinite. The Examiner also contends that it is not clear whether "a binding pocket" is determined by one amino acid, or a plurality of amino acids.

Applicants have overcome these rejections by amending the above-identified claims to clarify the invention. For example, amended claims 16 and 17 now recite a step of using all or part of a binding pocket, which comprises the

atomic coordinates of the amino acids that define the binding pocket, in an unphosphorylated JNK3 molecule to design or select an inhibitor of an unphosphorylated JNK3 molecule. Thus, applicants have removed any ambiguity as to what is meant by "a binding pocket" and have clarified what applicants regard as their invention. Applicants ask that the Examiner reconsider and withdraw the § 112 rejections.

The Examiner has rejected claim 20 contending that there is a lack of antecedent basis for the terms "prior to step a)," and requesting a clarification of the (1) metes and bounds of terms "JNK3 ... or JNK3 mutant molecule and a chemical entity," specifically whether the chemical entity is associated with both JNK3 and JNK3 mutant molecules, and (2) the metes and bounds of terms related to N-terminal and C-terminal deletions, specifically whether the deletions refer to both JNK3 and JNK3 mutant molecules.

Applicants have overcome these rejections by making claim 20 an independent claim by deleting the terms "prior to step a)," and by deleting the recitation to the terms "JNK3 mutant molecule" from claim 20. Thus, it is clear that in claim 20 the chemical entity is associated with unphosphorylated JNK3 and that the N-terminal deletion refers to unphosphorylated JNK3. Claim 21 depends from claim 20.

Applicants request that the Examiner reconsider and withdraw the § 112 rejection.

35 U.S.C. § 112, First Paragraph: Written Description

Claims 20 and 21 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserts that "the limitation of an N-terminal deletion of about 40 amino acids and a C-terminal deletion of about 20 amino acids has not been found in the specification." Applicants traverse.

In addition to Examples 1-6, the specification teaches an N-terminal deletion of about 40 amino acids and a C-terminal deletion of about 20 amino acids at page 6, line 29 to page 7, line 2. However, in order to expedite prosecution, applicants have amended claim 20 to recite "an N-terminal deletion of 39 amino acids" and have added claim 22 to further recite "a C-terminal deletion of 20 amino acids." The amendment to claim 20 and the addition of claim 22 is being made without waiver of applicants' rights to continue to prosecute and to obtain claims directed to the former subject matter either in this application or in other applications, including divisional or continuing applications, claiming benefit herefrom under 35 U.S.C. § 120. In view of these

amendments, applicants request reconsideration and withdrawal of the § 112 rejection.

35 U.S.C. § 112, First Paragraph: Enablement

Claims 16, 17 and 19-21 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that "the specification, while being enabling for a crystal structure and generating atomic coordinates of JNK3 without the first 39 residues, and JNK3 lacking the N-terminal 39 and C-terminal 20 residues, does not reasonably provide enablement for any JNK3 or JNK3 mutant molecule." In particular, the Examiner contends that the "instant specification does not provide enablement support for claims 16, 17, and 19-21 as directed to atomic coordinates from any JNK3. It is noted that said claims recite the limitation of 'according to Figure 1A.' However, said figure 'lists the atomic structure coordinates for unphosphorylated JNK3' (page 5, line 3). Therefore, said Figure 1A does not specifically support for any JNK3 molecule beyond the disclosed unphosphorylated JNK3." The Examiner further asserts that "the instant specification does not provide enablement support for claims 20 and 21 as directed to any JNK3 molecule beyond the disclosed JNK3 crystal." In particular, the Examiner purports that "it is, therefore,

unreasonable to expect one skilled in the art to use the information disclosed for specific crystals to make other [crystals] of predictable quality to practice the method of the claimed invention without undue experimentation."

Applicants traverse.

As an initial matter, independent method claims 16 and 20 differ from each other in that claim 20 comprises the step of producing a crystal whereas claim 16 does not. Therefore, it is applicants' understanding that the Examiner's comments directed to protein crystallization as an unpredictable art would apply only to the Examiner's rejection of claim 20 and claims dependent therefrom, i.e., claims 21 and 22.

Applicants have amended claims 16 and 20 to recite the term "unphosphorylated" JNK3 molecule, which clarifies that the atomic coordinates of the binding pocket according to Figure 1A are those associated with unphosphorylated JNK3. Claim 16 provides the step of using the binding pocket in the unphosphorylated JNK3 to design or select an inhibitor, whereas claim 20 also provides the step of determining the atomic coordinates of the specific amino acids that comprise the binding pocket in the unphosphorylated JNK3. The instant specification is the first to teach and enable the use of

specific, stable amino acid binding domains for design of inhibitors, agonists and antagonists to unphosphorylated JNK3. Using the coordinates of these same amino acids in any unphosphorylated JNK3 protein will lead to inhibitor, agonist and antagonist candidates for use in drug design. Because applicants have taught a method of using the precise atomic coordinates of the relevant amino acids comprising the unphosphorylated JNK3 binding pocket, claims 16 and 20 and those dependent therefrom meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

In applicants' response to the February 10, 2004 Office Action, applicants referred to a 2003 Scapin et al. article ("Scapin") and indicated that it combined the protein purification protocols and crystallization conditions disclosed in the present application with the knowledge of one skilled in the art at the priority of date of the instant application to crystallize and determine the structure of JNK3 in complex with several classes of inhibitors. However, on closer inspection of this document, applicants note that three out of four crystal complexes were obtained by soaking the crystals with inhibitors 1, 2 and 4, whereas one crystal complex was obtained by co-crystallization of JNK3 with inhibitor 3 (see, e.g., page 711). Applicants hereby provide

a copy of Scapin in the accompanying Information Disclosure Statement filed under 37 C.F.R. § 1.97(d).

Irrespective of Scapin, the present specification enables the production of crystals comprising a JNK3 protein and a chemical entity. However, in order to advance prosecution in the present application, applicants have amended the step of producing a crystal in claim 20 to recite "an unphosphorylated JNK3 molecule" and an "N-terminal deletion of 39 amino acids." Applicants make these amendments without waiver of applicants' rights to continue to prosecute and to obtain claims directed to the previous subject matter either in this application or in other applications, including divisional or continuing applications, claiming benefit herefrom under 35 U.S.C. § 120.

Furthermore, the Examiner acknowledges that applicants have disclosed information to enable one skilled in the art to produce crystals of a JNK3 without the N-terminal 39 residues, and a JNK3 lacking the N-terminal 39 and C-terminal 20 residues, and have generated atomic coordinates from said crystals for practicing the claimed invention in the context of identifying inhibitors. However, the Examiner asserts that one of skill in the art is "not enabled to practice the claimed invention as directed to identifying both

an agonist and an antagonist of a molecule comprising a binding pocket in the JNK3 molecule or JNK3 mutant molecule with the same binding pocket atomic coordinates." Applicants disagree. However, in order to advance prosecution, applicants have amended claims 16-17 and 19-21 to be directed to identification of an inhibitor. Applicants make this amendment without waiver of applicants' rights to continue to prosecute and to obtain claims directed to the previous subject matter either in this application or in other applications, including divisional or continuing applications, claiming benefit herefrom under 35 U.S.C. § 120.

In view of the above amendments and discussion, applicants request withdrawal of the 35 U.S.C. § 112, first paragraph, enablement rejections of claims 16, 17 and 19-21.

35 U.S.C. § 103(a): Obviousness

Claims 16, 17 and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Su et al. (US 6,162,613 A) in view of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983). The Examiner asserts that "Su et al. discloses a method for identifying an inhibitor (agonist or antagonist) of JNK3 (claim 6)." The Examiner further asserts that "even though the method disclosed by Su et al. does not

specify that the atomic coordinates of JNK3 according to Figure 1, the specific limitations of atomic coordinates in this instant case do not distinguish the invention from the prior art in terms of patentability because they are descriptive nonfunctional subject matter." The Examiner cites *In re Gulack* and MPEP §2106(IV)(B)(b) for the definition of nonfunctional descriptive material. Applicants traverse.

The subject matter sought to be patented in the present application would not have been obvious to one of skill in the art at the time of filing the present application given the teachings of Su et al. in view of *In re Gulack*. Su et al. generally teaches (1) taking a known serine/threonine or tyrosine kinase ("kinase-1") crystallized with a known inhibitor (or compound) to its ATP-binding site; (2) identifying the amino acids that comprise close contacts between the known inhibitor and ATP-binding site of kinase-1; (3) aligning some but not all of the amino acids of kinase-1 ATP-binding site with amino acids of a different serine/threonine or tyrosine kinase ("kinase-2"); (4) altering the amino acids of the identified kinase-2 ATP-binding site to produce a mutant serine/threonine or tyrosine kinase ("mutant-kinase-2"); (5) determining which mutant-kinase-2 molecule binds the known inhibitor with greater affinity over that of

the kinase-2 molecule; and (6) using this information (via molecular modeling) to alter the known inhibitor to create a *new* inhibitor to the kinase-2 molecule with greater binding affinity than that of known inhibitor. Independent claim 1 of Su et al. generally recites these steps and dependent claim 2 identifies the kinase-1 and kinase-2 of claim 1 as mitogen activating protein (MAP) kinases. Claim 6 of Su et al. depends from claim 2 and further defines kinase-2 as ERK2 or JNK3.

Amended claims 16-17 and 19-21, and added claim 22, are directed to unphosphorylated JNK3 or JNK3 mutant molecules. Su et al. neither discloses nor suggests an unphosphorylated JNK3 or JNK3 mutant molecule as the kinase-2 molecule. Furthermore, in contrast to the teachings of Su et al., the present invention teaches for the first time the crystal structure of unphosphorylated JNK3 and the specific contacts, i.e., the recited set of amino acids that comprise the binding pocket of unphosphorylated JNK3 or JNK3 mutant molecule, that may be used to design inhibitors of JNK3. Designing inhibitors using the actual structural coordinates of the unphosphorylated JNK3 binding pocket is more preferable than using the kinase-1, kinase-2, and mutant-kinase-2 approach taught by Su et al. On the other hand, if the

structure coordinates of the JNK3 protein were not available, then the method taught by Su et al. would provide a different and unrelated route for inhibitor drug design. Therefore, the teaching of the present invention cannot be obvious in view of Su et al. because Su et al. does not teach or suggest the specific binding pocket of a crystallized unphosphorylated JNK3 or JNK3 mutant molecule.

Moreover, contrary to the Examiner's assertion, the specific limitations of atomic coordinates in the instant application are descriptive functional subject matter under the holding in *Gulack*. In *Gulack*, the claims recited three key elements: (1) a *band*, ring or set of concentric rings; (2) a plurality of individual *digits* imprinted on the band or ring at regularly spaced intervals; and (3) an *algorithm* by which the appropriate digits are developed. The issue according to the *Gulack* court was whether there existed any new and unobvious functional relationship between the printed matter and the substrate. The *Gulack* court held there to be a functional relationship between the printed matter and the substrate because the claims at issue required a particular sequence of digits to be displayed on the outside surface of a band. For example, the court noted that the digits were related to the band in that (1) the band supports the digits

and (2) there is an endless sequence of digits, where each digit resides in a unique position with respect to every other digit in an endless loop. Therefore, an unobvious functional relationship existed.

Applicants believe that *Gulack* supports the patentability of the pending claims because a functional relationship exists between the computer and data stored therein - the computer converts novel structure coordinates (that were not available prior to this invention) into a display of a novel three-dimensional representation of a binding site of an unphosphorylated JNK3 protein. Such display could not be accomplished without the structural data and the ability of the computer to convert that data into said three-dimensional representation. By analogy, the sequence of numbers in *Gulack* are equivalent to the arrangement of atoms in the structure coordinates. Only when the particular arrangement of atoms (sequence of digits in *Gulack*) is used, can a three-dimensional representation of a binding site of an unphosphorylated JNK3 be produced. Therefore, as in *Gulack*, the present invention is claimed in terms of functional descriptive material.

Furthermore, the present claims require the skilled practitioner to use the binding pocket coordinates to design

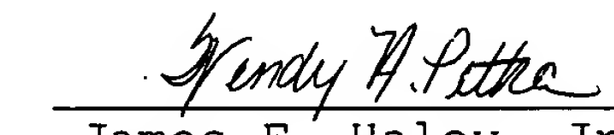
or select an inhibitor. For example, this may require the practitioner to visually inspect shape complementarities and/or follow the docking of the inhibitor by molecular dynamics or energy minimization and make adjustments accordingly. Ultimately, the computing processes are not performed in vacuo - they require interaction and participation of the skilled artisan.

In view the above arguments, applicants request the Examiner withdrawal the rejection of claims 16, 17 and 19 under 35 U.S.C. §103.

CONCLUSION

Applicants respectfully request that the Examiner reconsider and withdraw all outstanding objections and rejections, enter the amendments, and pass the resulting claims to allowance.

Respectfully submitted,



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